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REVIEW ARTICLE

Update on Medical Treatment of Cushing's Syndrome

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Abstract

First-line treatment of endogenous Cushing's syndrome (CS) is surgical removal of the tumor responsible for cortisol excess. However, medical therapy has an established role in treatment when patients are not surgical candidates or decline surgery, residual or recurrent disease is present and not amenable to repeat resection, and control of hypercortisolism is needed either preoperatively or while awaiting the effects of radiotherapy. The approach to medical therapy should be tailored based on the etiology, degree of hypercortisolism, and patient characteristics. Currently available medical therapy for all etiologies of CS either blocks adrenal production of cortisol or blocks its action at the level of the glucocorticoid receptor. Currently available medical therapy for Cushing's disease (CD) targets the adrenocorticotropic hormone-secreting pituitary tumor through activation of somatostatin and dopamine receptors, alkylating DNA damage, or immune system activation. More focused therapy with greater efficacy and fewer adverse effects is needed, particularly in the case of CD, with potential targets and drugs identified and in development.

Key Points

Medical therapy is needed for endogenous Cushing's syndrome (CS) when patients are not candidates for or decline surgery, when residual or recurrent disease is present and inoperable, and when control of hypercortisolism is needed preoperatively or while awaiting the effects of radiotherapy.

Currently available medical therapy for CS falls into three classes of medications: pituitary-directed agents, steroidogenesis inhibitors, and glucocorticoid receptor antagonists.

With respect to Cushing's disease, novel therapy is needed with new drugs under investigation targeting the adrenocorticotropic hormone receptor and genetic alterations associated with the corticotroph adenoma.

1 Introduction

Endogenous Cushing's syndrome (CS) is a serious medical condition resulting from chronic hypercortisolism with a wide range of metabolic, cardiovascular, immune, thrombotic, and neuropsychiatric morbidities [1, 2]. Diagnostic delay is common with important clinical repercussions contributing to increased morbidity and mortality with impaired quality of life, which advocates for prompt diagnosis and treatment [1, 3–5]. Possible etiologies with their frequencies include excessive secretion of adrenocorticotropic hormone (ACTH) by a corticotroph pituitary adenoma termed Cushing's disease (CD) (70%), dysregulated cortisol production from unilateral or bilateral adrenal lesions (20%), and ectopic production of ACTH or more rarely corticotropin-releasing hormone (CRH) by non-pituitary neuroendocrine tumors (10%) [1, 6]. The goals of treatment

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in CS are restoration of normal cortisol secretion, symptomatic improvement, and prevention of or improvement in comorbidities [7]. The first-line treatment for CS is surgical removal of the tumor responsible for the endogenous hypercortisolism [7]. Medical therapy may be used as the initial treatment modality preoperatively or as second-line treatment when patients are not surgical candidates or decline surgical intervention [7, 8]. Additionally, medical therapy plays an important role in residual or recurrent disease. This is particularly frequent in CD, with remission rates following transsphenoidal surgery of 60% and 80% for macroadenoma and microadenoma, respectively (in the hands of an experienced surgeon), and especially when repeat resection is not possible [8, 9]. Medical therapy is also used as a bridge to control hypercortisolism while awaiting the effects of radiotherapy [8, 9]. In this review, we aim to summarize indications for medical therapy in CS, currently available medications, and new targets and drugs in development.

2 Drug Categories

2.1 Pituitary-Targeting Therapy

Currently available drugs for treatment of CD targeting the corticotroph adenoma activate somatostatin and dopamine receptors, cause alkylating damage, or activate the immune system against it (Table 1) [8, 10].

2.1.1 Pasireotide

Pasireotide is a second-generation multi-receptor–directed somatostatin ligand with high affinity to four of five known subtypes of somatostatin receptors, especially somatostatin receptor subtype 5 (SSTR5) [11], which is abundantly expressed in ACTH-secreting corticotroph adenomas; unlike somatostatin receptor subtype 2 (SSTR2), SSTR5 is resistant to hypercortisolism-induced downregulation [12]. Daily subcutaneous pasireotide was approved in Europe and the USA for the treatment of CD in 2012 followed by several other countries after a phase 3 study including twice-daily 600-µg and 900-µg arms showed urinary free cortisol (UFC) normalization in 15% and 26% of the participants, respectively, after 6 months of treatment [13]. Association of UFC reduction and clinical signs of improvement, especially in blood pressure, lipid profile, weight, and waist circumference, was demonstrated [14]. Long-term efficacy was proven in an open-label, five-year extension of the phase 3 study, in which the median percentage change in UFC was preserved between 12 months and 5 years of treatment [15]. Beginning in 2017, monthly intramuscular pasireotide was approved by regulatory agencies in selected nations following a double-blind, randomized trial with two treatment arms (10 mg and 30 mg), which were equally effective for the treatment of CD, with UFC normalization in about 40% of participants in each treatment arm after 7 months. This effect persisted in an unblinded extension study with a median treatment period of 23.9 months [16, 17]. In both phase 3 trials, baseline UFC levels were negatively correlated with treatment response and disease control [13, 16]. Among treatment responders, UFC reduction occurred early and rapidly in 1–2 months. After 2 months of treatment, 92% and 89% of participants with uncontrolled hypercortisolism remained unchanged after 6 and 12 months of treatment, respectively [13, 16]. Daily pasireotide had a significant effect on tumor volume with mean volume reduction in 12 months of 43.8% in the 900-µg twice-daily arm but not in the 600-µg twice-daily arm [13]. Association of dosage and tumor volume reduction was not demonstrated with once-monthly pasireotide, in which 43% and 47% of participants had ≥ 20% reduction in tumor maximal diameter in the 10-mg and 30-mg study arms, respectively [16]. In another real-world, small study, no significant association was found between disease control and tumor shrinkage [18]. Pasireotide adverse events (AEs) include somatostatin analog class gastrointestinal and biliary adverse effects but also a high frequency of hyperglycemia and diabetes mellitus as a result of decreased incretin and insulin secretion [13]. In the phase 3 study of daily subcutaneous pasireotide, cholelithiasis was found in 30% of participants without dose effect, while in the phase 3 study of long-acting pasireotide, 45% of participants in the 30-mg arm had cholelithiasis versus 20% of participants in the 10-mg arm [13, 16]. Despite the high frequency of cholelithiasis, symptoms and surgical intervention were comparatively rare [13, 16, 17]. With respect to gastrointestinal adverse effects, long-acting pasireotide demonstrated possible advantage with a 12-month incidence of diarrhea 39% versus 58%, nausea 21% versus 52%, and abdominal pain 15% versus 24% for the monthly versus daily formulation, respectively [13, 16]. Hyperglycemia-related AEs occurred in 70% to 80% in the pivotal studies as well as in a real-world study, including diabetes worsening and progression from normoglycemia to prediabetes and diabetes but without cases of diabetic ketoacidosis or hyperosmolar hyperglycemia [13, 16, 19]. In the phase 3 studies, about 5–6% of participants discontinued the treatment due to hyperglycemia-related AEs [13, 16]. The recommended treatment for pasireotide-related hyperglycemia includes metformin as first-line and glucagon-like peptide-1 (GLP-1)-based therapy as second-line [20, 21]. Other rare but potentially serious reported AEs include liver toxicity, especially elevated γ-glutamyl transferase concentration (4–5%), prolonged QT, and bradycardia [16, 17]. The annualized rates of first AEs decline steadily during

Table 1 Drugs targeting the corticotroph adenoma for treatment of Cushing's disease (CD)

Drug	Dose	Efficacy	Evaluation before treatment initiation	Main adverse effects (%)
Pasireotide[a,b]	Initial dosing: SC 0.6–0.9 mg BID Dosage titration: dose elevation for patients started on 0.6 mg BID to 0.9 mg BID according to treatment response in 2 months according to tolerability [217]	15% and 26% of patients (600 or 900 μg BID, respectively) had UFC ≤ ULN after 6 months of treatment [13]. Patients who were controlled at month 12 on treatment remained so after 60 months of treatment [15]	Baseline levels of serum glucose, HbA1c, liver function tests, serum potassium, and serum magnesium Electrocardiogram [217]	Diarrhea (58%), nausea (52%), hyperglycemia (40%), cholelithiasis (30%), headache (28%), abdominal pain (24%), injection site reactions (17%), transaminitis (10%), QT prolongation (6%), bradycardia (< 5%) [217]
Pasireotide LAR[a,b]	Initial dosing: IM 10 mg once monthly Dosage titration: according to tolerability and treatment response [218]	28.4–37% of patients achieved UFC normalization after 7 months of treatment [16]. 53.1% stayed with UFC < ULN with an extension study [17]	Baseline levels of serum glucose, HbA1c, liver function tests, serum potassium, and serum magnesium Electrocardiogram [218]	Hyperglycemia (39.5%), diarrhea (34.6%), cholelithiasis (28.4%), nausea (22.2%), diabetes mellitus (18.5%), nasopharyngitis (17.3%), and abdominal pain (14.8%) [17]
Cabergoline	Dosage range as reported in the literature: PO 0.5–7 mg weekly typically in two divided doses, administered at bedtime, typical starting dose 0.5 mg BIW. Dosage titration: according to tolerability and treatment response [22, 30]	Reported remission rate (meta-analysis) 34%, median UFC reduction 32.2% [30, 31] Escape rate 18.2–38.9% [22]	N/A	Dizziness, gastrointestinal discomfort, loose stools, nausea, nasal congestion, visual hallucinations, personality change [22]
Temozolomide	PO 150–200 mg/m^2 for 5 consecutive days every 28 days. Evaluation of tumor response should be done after 3 cycles for decision about treatment continuation [37]	Among patients with ACTH-secreting tumors (10 carcinomas), 67% had reduction in ACTH and 56% reduction in tumor volume [36] In another study (mixed group of tumors), radiological response was complete response 9.6%, partial response 30.1%, stable disease 28.1%, and among patients with secreting tumors, 33.6% had at least 50% decreased hormone secretion [40]	Baseline levels of complete blood count and liver function tests. Scheduled monitoring is required during and after treatment cycles [37]	Fatigue (60%), nausea, vomiting (33%), myelosuppression (31%), opportunistic infections, and transaminitis. Hematological malignancies can occur years after treatment (< 1:10,000) [37]

ACTH adrenocorticotropic hormone, *BID* twice a day, *BIW* twice a week, *HbA1c* glycated hemoglobin, *IM* intramuscular, *PO* oral, *SC* subcutaneous, *UFC* urinary free cortisol, *ULN* upper limit of normal

[a]Drugs approved for treatment of CD in the European community

[b]Drugs approved for treatment of CD in the USA

long-term pasireotide treatment with most AEs occurring during the first month to first year [15, 17].

2.1.2 Cabergoline

Dopamine receptor type 2 (D2R) expression occurs in up to 80% of corticotroph adenomas without relation to tumor size, infrasellar or parasellar invasiveness, and degree of cortisol secretion [12, 22]. Dopamine agonist (DA) monotherapy for CD was studied in several small prospective and retrospective studies and a more recently published meta-analysis [23–31]. Cabergoline-treated patients had a 34% remission rate with a 22% long-term escape rate among those who entered remission [30, 31]. Cabergoline responders had significantly lower baseline UFC, were more likely to have a history of surgery, and had significantly longer therapy duration and lower cabergoline dosage (median 2 mg weekly, interquartile range 1–2.5 mg weekly), while age, gender, hyperprolactinemia, and basal ACTH were not associated with response [30, 31]. Adverse events were mostly mild and known from other treatment indications with gastrointestinal AE being the most frequent followed by asthenia. A few cases were reported with hypocortisolism requiring hydrocortisone treatment, and one case of tricuspid regurgitation progression from mild to moderate after two years of treatment [30, 31]. Although valvular disorders are a concern with long-term treatment with high doses of cabergoline, this association has been demonstrated mostly in patients treated for Parkinson disease with doses up to 25 mg weekly and is not clearly established in patients treated for pituitary tumors at lower doses [32]. Impulse control disorders are a recognized risk of DA therapy in prolactinomas [33]. While a similar risk in DA-treated patients with CD is not established and limited evidence to date suggests the risk may be low, vigilance is needed to monitor for impulsivity and worsening of underlying psychiatric disorders [34]. Of note, in one large retrospective multicenter study, cabergoline add-on therapy with ketoconazole was associated with a manic episode in a patient with a history of depression [29]. A growing body of evidence supports cabergoline safety during pregnancy, but successful treatment of CD in pregnancy by cabergoline was published in only a few case reports, so there is insufficient evidence to recommend its use [35].

2.1.3 Temozolomide

Temozolomide is an oral, second-generation alkylating agent, which induces DNA damage by attachment of methyl groups to guanine bases [36]. It is recommended as first-line treatment for aggressive pituitary tumors and carcinomas [37]. Temozolomide treatment is administered for three cycles then continued depending on radiological response [38]. In a German national survey of 19 patients with aggressive corticotroph adenoma/carcinoma treated with temozolomide, 10 had tumor regression, 4 had stable disease, and 3 had progressive disease. Median ACTH decreased from 42 pmol/L at baseline to a nadir of 23 pmol/L but rose after to 183 pmol/L [39]. In another study, 156 of 171 patients with aggressive pituitary adenoma/carcinoma were treated with temozolomide (30% ACTH-secreting tumors) with complete response in 9.6%, partial response in 30.1%, stable disease in 28.1%, and progressive disease in 32.2% [40]. The efficacy of temozolomide is limited by O^6-methylguanine-DNA-methyltransferase (MGMT), a DNA repair enzyme counteracting its antineoplastic action [8]. Epigenetic silencing of *MGMT* by promoter methylation was associated with more favorable response to temozolomide therapy in patients with newly diagnosed glioblastoma [41] but less so in pituitary adenomas with only 57% predictive value [36, 42]. The clinical value of MGMT measurement before treatment of aggressive pituitary tumors is controversial, and mutations in DNA mismatch repair genes may play a role in the response to temozolomide [38]. The current recommendation is to consider a trial of temozolomide even in the presence of high MGMT expression [37]. Temozolomide AEs are frequent and reported in 54% of patients, including nausea and vomiting, myelosuppression, abnormal liver function tests, and elevated risk of opportunistic infections (especially in patients exposed to glucocorticoids who develop leukopenia) [37]. There is a need to better define the ideal timing of temozolomide discontinuation after positive response as well as the utility of repeating treatment in the event of recurrence following discontinuation [38].

2.1.4 Immunotherapy

Immunotherapy is based on the ability of the immune system to suppress and cause regression of tumors [43]. Immune checkpoint inhibitors (ICIs) are a group of drugs which target T cell inhibitory ligands and receptors used by tumor cells to evade the immune system [43]. The occurrence of hypophysitis as an adverse effect of ICI treatment in 5–10% of patients supports a possible role of ICIs in the treatment of refractory pituitary tumors [44]. Current data regarding the effectiveness of ICIs in the treatment of aggressive corticotroph adenomas/carcinomas are limited to one retrospective cohort study, one small case series, and a few case reports [43, 45–52]. In a retrospective cohort study, 9 of 15 patients had corticotroph tumors (five aggressive pituitary adenomas and four carcinomas), and treatment with combination therapy of ipilimumab and nivolumab resulted in a partial response in three out of nine tumors, all carcinomas [51]. Other cases published so far include eight carcinoma cases and one aggressive adenoma, which were treated either with

pembrolizumab monotherapy or combination therapy of ipilimumab and nivolumab. Treatment results of the other cases include one case of complete response, three cases of partial response, two cases of stable disease, one case of rapid progressive disease, and one case of dissociative response with decrease in tumor mass and biochemical improvement but simultaneous emergence of new lesions [45, 46, 48–50, 52]. According to the limited data available, it seems that carcinomas are more responsive to ICI treatment than aggressive adenomas [51]. Prior temozolomide treatment might render the tumor more immunogenic and responsive to treatment due to mismatch mutations caused by temozolomide treatment [45]. Uncontrolled endogenous hypercortisolism has an immunomodulatory effect that might negate the treatment effect of ICIs, so it is recommended to achieve control of hypercortisolism prior to treatment [46]. Additionally, it should be noted that co-treatment with ketoconazole and nivolumab caused severe drug-induced liver injury necessitating discontinuation in one case report [47]. In summary, ICIs represent a promising treatment line for patients who progress on temozolomide therapy. Two ongoing clinical studies (NCT02834013, NCT04042753) will hopefully provide new information regarding the potential and proper usage of ICI treatment in CD [8].

2.2 Steroidogenesis Inhibitors

Steroidogenesis inhibitors inhibit the activity of one or more enzymes responsible for adrenal steroidogenesis and are the most widely used cortisol-lowering drugs for the treatment of CS (Table 2). Steroidogenesis inhibitors share several common characteristics: (a) they act rapidly, within hours to days, to lower cortisol secretion; (b) these drugs can be used with two main regimens: titration with a progressively increasing drug dosage according to cortisol levels, or using a "block and replace" strategy with an immediate high drug dosage to lower cortisol production to the range seen in adrenal insufficiency (AI) with subsequent addition of hydrocortisone (or other exogenous glucocorticoid) replacement [53, 54]; (c) they are usually more effective in ACTH-independent CS. In CD, there may be a compensatory increase in ACTH secretion, which can overcome the enzymatic blockade ("escape phenomenon") and require an increase in drug dosage; (d) they may be responsible for AI; (e) since these agents act on different target enzymes, combined treatment often results in a synergistic effect allowing better control of cortisol than with a single agent and allowing for lower doses of single agents to be used, reducing drug-related intolerance, and (f) they are usually contraindicated in pregnancy [7]; although, metyrapone has occasionally been used safely in a limited number of cases [55].

As with other drug classes, data on efficacy and tolerance of steroidogenesis inhibitors are mostly available for CD, the main etiology of CS. Importantly, to date, no prospective, randomized, head-to-head studies comparing the effectiveness and safety of steroidogenesis inhibitors are available.

2.2.1 Ketoconazole

Ketoconazole inhibits multiple steroidogenic enzymes including CYP17A1, CYP11A1, and CYP11B1 [56]. It is administered orally at a dose of 400–1200 mg daily in two to three divided doses. Reduction of gastric acidity with proton pump inhibitors may impair ketoconazole absorption. Its maximal effect is obtained after 2–3 days [57]. In the largest retrospective study of ketoconazole use in CD with 200 patients, UFC normalization occurred in 49% [58]. The relatively low average daily dosage used (700 mg) suggests frequent under-titration and underestimation of efficacy. A meta-analysis reported normalization of cortisol levels in 71% (95% CI 52–87%) in patients with various causes of CS [59]. A transient and mild increase in liver enzymes was seen during the first weeks of treatment in approximately 15%, while major idiosyncratic severe cytolytic hepatitis occurred in 2.5–5.5% [58, 60], making early and frequent measurement of liver enzymes mandatory. Liver enzymes usually return to normal within 2–4 weeks after discontinuation [7]. Inhibition of testicular steroidogenesis can induce male hypogonadism and gynecomastia, making the use of this drug preferable in women [56]. Importantly, ketoconazole is a potent inhibitor of CYP3A4 and has numerous drug-drug interactions [7]. Finally, QT prolongation is considered a possible risk, although it was not reported as an AE in the studies evaluating use of ketoconazole in CD [6, 54].

2.2.2 Levoketoconazole

As opposed to ketoconazole, which is a mix of two enantiomers (L- and D-forms), levoketoconazole is a pure L-enantiomer with increased half-life, increased in vitro potency, and reduced liver exposure compared to ketoconazole. However, in phase 3 studies [61, 62], mostly involving participants with CD, the response rate and safety (including hepatic tolerance) were roughly similar to that commonly observed in the clinic and reported in retrospective studies with ketoconazole. As with ketoconazole, levoketoconazole has an androgen-lowering effect. The risk of QT prolongation was approximately 10% in phase 3 studies, therefore electrocardiographic monitoring at baseline and during treatment is required [54, 61, 62].

2.2.3 Metyrapone

Metyrapone, which mainly inhibits CYP11B1 and CYP11B2 [56], is probably the fastest-acting steroidogenesis inhibitor with the nadir of serum cortisol obtained within 2 h

Table 2 Steroidogenesis inhibitors for treatment of Cushing's syndrome (CS)

Drug	Dose	Efficacy	Evaluation before treatment initiation	Main adverse effects (%)
Ketoconazole[a]	Initial recommended dosing for CD: PO 400–600 mg daily in two to three divided doses [7, 54, 67]. Dosage titration: according to tolerability and treatment response, up to 1600 mg daily. Larger starting doses (1000–1200 mg daily) have been used in the treatment of intense hypercortisolism [7, 54]	45–93% of patients with CD achieved UFC normalization in retrospective series [56]. 49% with UFC control in the largest retrospective study [58]	Baseline levels of liver function tests, serum sodium, and serum potassium Electrocardiogram. Check for proton pump inhibitors (impaired absorption of ketoconazole) and potential drug interactions	Transient and mild increase in liver enzymes (up to 15%), severe cytolytic hepatitis requiring treatment discontinuation (<5%), gastrointestinal disorders (13%), rash, male hypogonadism, gynecomastia, and QT prolongation [56, 58, 60]
Levoketoconazole	Initial recommended dosing: PO 300 mg daily in two divided doses. Dosage titration: according to tolerability and treatment response, up to 1200 mg daily [61, 62]	36–45% [61] and 50% at month 6 [62] (prospective randomized trials)	Baseline levels of liver function tests, serum sodium, and serum potassium. Eectrocardiogram. Check for potential drug interactions	Transient and mild increase in liver enzymes (15%), cytolytic hepatitis requiring treatment discontinuation (4%), gastrointestinal disorders (32%), headache (28%), and QT prolongation (10%) [61]
Metyrapone[a]	Initial recommended dosing for CD: PO 750–1000 mg daily in three divided doses [7, 54, 67]. Dosage titration: according to tolerability and treatment response, up to 4000 mg daily. Larger starting doses (1500–2500 mg daily) have been used in the treatment of intense hypercortisolism [54, 64, 65]	45–100% remission rates in CD reported with mean 71% [56], 66% control in a meta-analysis [219]. 43 and 55% UFC and serum cortisol control, respectively, in the largest retrospective study [64]	Baseline levels of serum sodium and potassium. Electrocardiogram	Nausea, dyspepsia (23%), hirsutism/acne (36%), dizziness (30%), hypokalemia, and hypertension (10%) [56]
Osilodrostat[a,b]	Initial recommended dosing for CD: PO 2 mg daily in two divided doses. Dosage titration: according to tolerability and treatment response, up to 30 mg BID. Larger starting doses (10–60 mg daily) have been used in the treatment of intense hypercortisolism [75, 76]	67–81% (prospective randomized trials) [71, 72]	Baseline levels of serum sodium, potassium, and magnesium. Electrocardiogram. Baseline blood pressure and number of antihypertensive medications	Nausea (41%), adrenal insufficiency (26–29%), hypokalemia, hypertension, edema (10–15%), and hirsutism/acne in women (10%) [71, 72]
Etomidate	IV infusion with various protocols: from low/intermediate doses (0.02–0.08 mg/kg/h) with titration based on serum cortisol [82–84] to high dosage 2.5 mg/h and up to 4 mg/h in a block and replace strategy [56, 83]	Control of hypercortisolism in up to 100% of patients (small series) [56, 82–84]	Electrocardiogram. Baseline levels of cell blood count, renal function, serum sodium, and serum potassium	Sedation at high dosage requiring administration in an ICU, nausea, nephrotoxicity, myoclonus, and lactic acidosis at high dosage

Table 2 (continued)

Drug	Dose	Efficacy	Evaluation before treatment initiation	Main adverse effects (%)
Mitotane	PO 0.5–1.5 g daily in two to three divided doses with meals in the majority of patients reported in the largest published cohort [85]. Dosage titration: according to tolerability, cortisol levels, and circulating mitotane concentrations (target = 8.5 mg/L), up to a mean daily dose of 2.6 g (1.0–6.0) [85]	Delayed control in 72–100% of patients [56, 85] (adrenal insufficiency and block and replace strategy in the largest published cohort [85])	Pregnancy test in female patients of reproductive potential. Electrocardiogram. Baseline levels of liver function tests and plasma lipids. Check for potential drug interactions	Gastrointestinal disorders (47%), asthenia/dizziness, cognitive disorders (30%), hypercholesterolemia (71%), increased GGT (47%), gynecomastia/male hypogonadism (17%), and skin rash (6%) [85]

BID twice a day, *CD* Cushing's disease, *GGT* γ-glutamyl transferase, *ICU* intensive care unit, *IV* intravenous, *PO* oral, *UFC* urinary free cortisol

[a]Drugs approved for treatment of CS in the European community

[b]Drugs approved for treatment of CS in the USA

following a single dose [63]. Due to its short half-life, metyrapone should be administered in three to four daily divided doses. In a large retrospective survey, control of hypercortisolism in various causes of CS was reported in approximately 50% with an average daily dosage of 1350 mg, suggesting under-titration and underestimation of treatment efficacy [64]. In the two largest single-center series reported, cortisol levels were normalized in up to 70–81% of patients with CS of various etiologies [65, 66], while in the largest retrospective study, control of UFC and mean serum cortisol "day-curve" was achieved in 43% and 55% of patients, respectively. Nausea and abdominal discomfort are the most frequently reported AEs. The accumulation of mineralocorticoid precursors upstream from the 11β-hydroxylase blockade may result in edema, hypokalemia, and hypertension, while accumulation of the adrenal androgen δ4-androstenedione may result in hirsutism and acne in women [56]. The increase in the immediate cortisol precursor 11-deoxycortisol may lead to an overestimation of cortisol levels in some immunoassays, potentially masking normalization of cortisol levels and biochemical hypoadrenalism [67, 68]. Elevations in ACTH are frequent and may contribute to treatment escape in up to 18% while also leading to overproduction of androgen and mineralocorticoid precursors [56]. With respect to medical therapy in pregnancy, use of metyrapone for every etiology of hypercortisolism may be considered based on a limited number of cases with reported risks of worsening hypertension in the setting of deoxycorticosterone accumulation and impaired fetal steroidogenesis in the setting of crossing the placental barrier [55].

2.2.4 Osilodrostat

Osilodrostat inhibits CYP11B2 and CYP11B1 activity with an enhanced potency and prolonged half-life compared to metyrapone [69]. Historically, it was initially developed as a possible treatment for hypertension and primary aldosteronism [70]. In prospective, randomized, phase 3 studies conducted in participants with CD, UFC normalization occurred in up to 81% after 12 weeks with sustained control [71, 72]. Extension studies of LINC 3 and LINC 4 showed long-term efficacy without escapes as well as sustained clinical improvement [73, 74]. Only a few retrospective studies have reported on the efficacy of osilodrostat in other etiologies of CS [75, 76]. The most common AEs included nausea, abdominal discomfort, and similar to metyrapone, side effects related to accumulation of steroids upstream of the enzymatic blockade, such as hypokalemia, hypertension, and hirsutism in women, occurring in approximately 15% of patients. Interestingly, steroid precursor levels decrease and may even normalize in some patients during long-term treatment, despite sustained increased circulating ACTH

levels, suggesting that osilodrostat, unlike metyrapone, acts on target enzymes other than CYP11 [69, 73, 77]. Additionally, in comparison to metyrapone, osilodrostat may result in greater blood pressure reduction during short-term treatment [78]. Due to its potency, AI occurs in roughly one-third of patients receiving osilodrostat [71]; therefore, it should be anticipated with regular testing of early morning serum cortisol with appropriate patient education concerning temporary drug withdrawal and hydrocortisone supplementation. Importantly, AI may occur months after commencing treatment [79], making a reduction in drug dosage possible, while intriguing cases of prolonged AI greater than 6 months after osilodrostat withdrawal have also been described [80, 81].

2.2.5 Etomidate

Etomidate is an anesthetic drug administered intravenously, which rapidly inhibits CYP11B1 and can be used for short-term treatment when the oral route is impossible. Several protocols using a titration procedure or a "block and replace" regimen have been described [82–84]. Relatively high dosages induce a degree of sedation and thus require intensive care unit (ICU) hospitalization.

2.2.6 Mitotane

Mitotane is an adrenolytic drug used for the treatment of adrenocortical carcinoma (ACC). At relatively moderate dosage (2–3 g per day), mitotane inhibits multiple steroidogenic enzymes, ultimately leading to AI requiring hydrocortisone supplementation [85]. However, the anti-cortisol effect is usually delayed for months making mitotane use unsuited for the rapid control of hypercortisolism, except for when used in combination therapy [85, 86]. These characteristics, together with the frequency of side effects and its off-label use in causes of CS other than ACC, limit its use [7].

2.3 Glucocorticoid Receptor Antagonists

Medical therapy targeting the glucocorticoid receptor (GR) in CS represents a potential management tool, irrespective of the etiology of hypercortisolism, in which the goal is not to decrease cortisol secretion but rather blunt its effects through GR blockade (Table 3) [6].

2.3.1 Mifepristone

Mifepristone is an oral, nonselective progesterone receptor (PR) and GR antagonist with an affinity for the GR approximately 10-fold and 4-fold higher than that of cortisol and dexamethasone, respectively [6, 87–89]. It was approved in the USA in 2012 for the treatment of CS in patients with type 2 diabetes mellitus (T2DM) or glucose intolerance who are not surgical candidates or who do not experience surgical cure [6, 90, 91]. Given cortisol levels are not expected to decrease with GR antagonist therapy, response to therapy must be assessed clinically, as biochemical cortisol markers have no utility [89, 92].

Over the past 15 years, clinical studies and trials have established mifepristone's efficacy in the treatment of CS while highlighting its possible adverse effects and important clinical considerations [6, 89, 92]. The pivotal Study of the Efficacy and Safety of Mifepristone in Endogenous CS (SEISMIC) trial was a phase 3, open-label investigation of treatment with mifepristone at doses of 300–1200 mg daily (mean 732 mg) over 6 months in 50 participants with CS and T2DM, impaired glucose tolerance (IGT), or hypertension [93]. The primary end points of a 25% or greater decrease in area under the curve for glucose on oral glucose tolerance testing was met in 60% of participants with T2DM/IGT and a ≥ 5 mmHg decrease in diastolic blood pressure was met in 38% of participants with hypertension [93]. Additional improvements in weight, waist circumference, depression, cognition, and quality of life were seen with 87% demonstrating overall clinical improvement [93]. In the long-term extension study, over 80% of participants who continued mifepristone for up to 3.5 years demonstrated sustained clinically meaningful weight loss of 5% or greater [94].

The most common adverse effects of mifepristone relate to its underlying mechanism of GR and PR blockade [89]. Compensatory increases in ACTH and cortisol, particularly in CD, may overwhelm the ability of renal 11β-hydroxysteroid dehydrogenase type 2 to inactivate cortisol resulting in clinical manifestations of mineralocorticoid excess, such as hypokalemia, hypertension, and peripheral edema [93, 95]. As such, consensus recommendations are to correct hypokalemia and optimize hypertension management prior to initiation with preferential use of spironolactone [92]. Symptoms of glucocorticoid withdrawal related to rapid GR blockade are likely, especially early on in treatment [6, 89]. It can be particularly challenging to differentiate glucocorticoid withdrawal from AI with GR antagonist therapy, as cortisol levels are not expected to decrease and the diagnosis of AI must be made clinically [89]. Related to its PR antagonism, mifepristone is associated with endometrial thickening; although, current understanding is that mifepristone-induced endometrial changes are benign without malignant potential [93, 96, 97].

Pregnancy is an absolute contraindication with a negative pregnancy test required before treatment initiation in female patients of reproductive potential and in the event of therapy interruption for greater than 14 days [90]. Mifepristone is a CYP3A4 and CYP2C8/2CP inhibitor, and as such,

Table 3 Glucocorticoid receptor antagonists for treatment of Cushing's syndrome (CS)

Drug	Dose	Efficacy	Evaluation before treatment initiation	Main adverse effects (%)
Mifepristone[a]	Initial dosing: PO 300 mg once daily Dosage titration: 300 mg increments every 2–4 weeks Dose range: 300–1200 mg once daily (maximum 600 mg once daily in renal impairment and mild to moderate hepatic impairment, use in severe hepatic impairment not recommended) Should be taken with food [90]	In SEISMIC, there was a 25% or greater decrease in area under the curve for glucose on oral glucose tolerance testing in 60% of patients with T2DM/IGT and a 5 mmHg or greater decrease in diastolic blood pressure in 38% of patents with hypertension [93] Additional improvements were seen in weight, waist circumference, depression, cognition, and quality of life leading to overall clinical improvement in 87% [93]	Baseline blood pressure, serum glucose, HbA1c, serum potassium, serum creatinine, liver function tests, electrocardiogram, pregnancy test in female patients of reproductive potential, and thyroid function tests [89, 90, 92]. Check for potential drug interactions [89, 92]	Nausea (48%), fatigue (48%), hypokalemia (44%), headache (44%), endometrial thickening (38%), arthralgia (30%), vomiting (26%), peripheral edema (26%), hypertension (24%), dizziness (22%), decreased appetite (20%), adrenal insufficiency (17%), vaginal bleeding (14%) [93, 94]
Relacorilant	100–400 mg once daily [98, 100]	In GRACE, mean decrease in systolic blood pressure of 7.9 mmHg and in diastolic blood pressure of 5.4 mmHg, mean decrease in area under the curve for glucose on glucose tolerance testing of − 3.3 h*mmol/L and mean decrease in HbA1c of 0.3 [101]	Baseline blood pressure, serum glucose, HbA1c, and serum potassium	Nausea (34%), peripheral edema (33%), extremity pain (30%), back pain (27%), fatigue (22%), and arthralgia (20%) [102]

HbA1c glycated hemoglobin, *IGT* impaired glucose tolerance, *PO* oral, *T2DM* type 2 diabetes mellitus

[a]Drugs approved for treatment of CS in the USA

drug-drug interactions are likely with established consensus recommendations for management [89, 92]. Additionally, QT prolongation occurs in a dose-dependent manner [89, 90]. Other QT prolonging medications should be avoided, or if necessary, used at the lowest effective dose possible [89, 90]. Mifepristone should not be used in patients requiring high-dose exogenous glucocorticoid treatment for comorbid conditions [92].

2.3.2 Relacorilant

Relacorilant is a novel, oral, selective GR antagonist without significant affinity for the PR currently undergoing clinical investigation for use in CS [6]. In a phase 2, multicenter, dose-finding clinical trial with 35 participants, relacorilant demonstrated efficacy in improving clinical parameters of glucose tolerance, blood pressure, body weight, liver function, coagulability, quality of life, and cognition with suggestion of a dose response effect without adverse effects of hypokalemia or vaginal bleeding [98]. The observed smaller increases in cortisol and ACTH are postulated to explain the absence of hypokalemia with relacorilant as compared to mifepristone [98]. Indeed, an in vitro study in the mouse corticotroph tumor cell line AtT20 demonstrated that dexamethasone-induced suppression of proopiomelanocortin (POMC) expression and ACTH release was prevented more potently by mifepristone compared to relacorilant [99]. This may indicate that both drugs have a different mode of action on the corticotroph tumor cell with respect to negative feedback inhibition.

The phase 3 Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE) study with 152 participants with CS (~78% ACTH-dependent) with hypertension and/or T2DM/IGT consisted of an initial 22-week, open-label phase of relacorilant 100 mg daily titrated up to 400 mg daily as tolerated followed by a 12-week, double-blind, placebo-controlled, randomized-withdrawal phase in which those participants meeting clinical response criteria at the end of the open-label phase received either placebo or continued relacorilant at the same dose [100, 101]. In the open-label phase, rapid and persistent improvements in hypertension and hyperglycemia were seen [101]. In the randomized-withdrawal phase, participants continuing relacorilant were less likely to lose hypertension control as compared to the placebo group (OR 0.17) [101]. Additionally, participants continuing relacorilant maintained glycemic measures with no significant increase in the mean area under the curve for glucose on oral glucose tolerance testing and glycated hemoglobin, unlike in the placebo group [102]. No increases in cortisol, hypokalemia, and AI were observed [102]. No cases of vaginal bleeding and endometrial thickening were reported [102]. As in earlier studies, relacorilant was not associated with QT prolongation [102, 103]. Figure 1 illustrates the three drug categories used for treatment of CS.

3 Medical Therapy According to Etiology

3.1 Cushing's Syndrome Based on Corticotroph Adenomas

Although CD should be treated ideally with drugs targeting the corticotroph adenoma, medical therapy for these patients usually starts with steroidogenesis inhibitors due to the mild-moderate efficacy and potential side effects of pituitary-targeting drugs [2, 9]. In particular, one is hesitant to use pasireotide considering its hyperglycemic effects [13, 16, 19]. On the other hand, pasireotide can induce tumor shrinkage, which may be beneficial in a subset of patients [9, 13]. The steroidogenesis inhibitor osilodrostat has been investigated in large phase 3 trials and has shown efficacy of up to 80% in terms of UFC normalization in CD [71, 72].

In patients with moderate-severe hypercortisolism, there is rationale for combination therapy with drugs with complimentary mechanisms of action or combination therapy with pituitary- and adrenal-targeting drugs, which might offer higher rates of long-term remission with lower medication doses and less AEs [27]. Corticotroph adenomas often co-express SSTR5 and D2R, and simultaneous targeting of these receptors may have synergistic effects [12, 104]. A sequential regimen of pasireotide followed by cabergoline as an add-on was tried in two studies [11, 105]. In the larger and more recent study, 0.5–1 mg daily cabergoline was added to 900-µg twice-daily pasireotide if the UFC levels remained above the upper limit of normal after 16 weeks of treatment. In this study, 17 of 68 patients achieved UFC normalization with pasireotide monotherapy, with addition of 17 more patients achieving UFC normalization with combination therapy. Hyperglycemia and nausea were the most common AEs [11]. In the second and smaller study, a sequential regimen of pasireotide followed by cabergoline and then ketoconazole, according to need, was studied in 17 patients for 80 days with 5 of 17 patients achieving UFC normalization on pasireotide monotherapy with addition of four and six patients after cabergoline and ketoconazole were added sequentially [105]. In another study, addition of low-dose ketoconazole to cabergoline increased the remission rate from 25 to 75% [25]. No clear benefit favoring a specific sequence of combination treatment was shown [27], and escape phenomenon was reported also in combination therapies of cabergoline and steroidogenesis inhibitors (2 of 4 patients) [29] as well as pasireotide and cabergoline (13 of 21 patients) [11].

As outlined in the section Pituitary-Targeting Therapy, temozolomide and immunotherapy can be used for patients

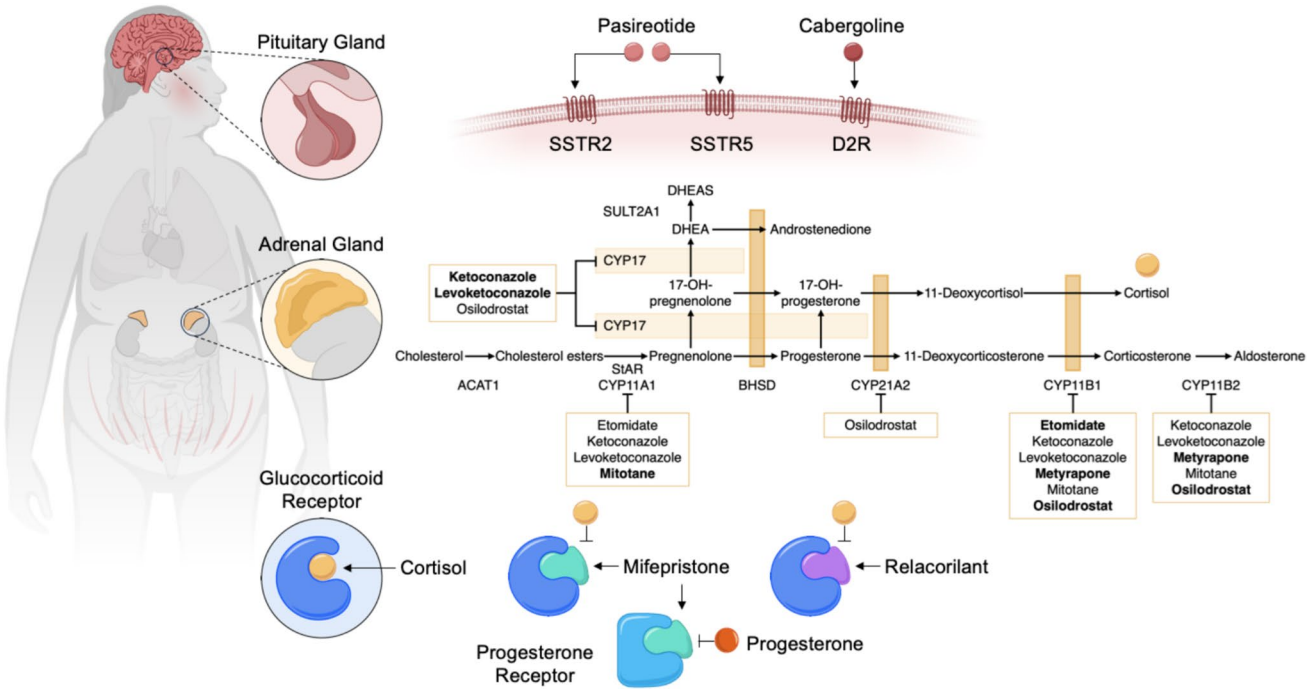

Fig. 1 Medical therapy for the treatment of Cushing's syndrome. The three main classes of medications are pituitary-directed agents, steroidogenesis inhibitors, and glucocorticoid receptor antagonists. Pasireotide preferentially binds to somatostatin receptor subtype 5 (SSTR5) compared to somatostatin receptor subtype 2 (SSTR2), while cabergoline activates dopamine receptor type 2 (D2R) in the corticotroph tumors decreasing adrenocorticotropic hormone (ACTH) secretion. Ketoconazole, levoketoconazole, osilodrostat, metyrapone, etomidate, and mitotane decrease cortisol synthesis by inhibiting different enzymes in the adrenal steroidogenesis pathway. Each steroidogenesis inhibitor is bolded over their principal sites of action. Mifepristone and the newer drug relacorilant are competitive glucocorticoid receptor antagonists and exert their effects by blocking the biological effects rather than secretion of cortisol. While mifepristone is a competitive progesterone receptor antagonist, relacorilant is a selective glucocorticoid receptor modulator with no progesterone activity

with aggressive corticotroph tumors. Successful treatment of aggressive corticotroph adenomas and carcinomas with temozolomide in combination with pasireotide has been reported. In one case of a widely metastatic ACTH-secreting pituitary carcinoma refractory to repeated surgical intervention, bilateral adrenalectomy, medical therapy, and radiotherapy, combination therapy with temozolomide and pasireotide for 12 months followed by pasireotide monotherapy for 9 months was associated with successful tumor stabilization and control of ACTH secretion [106]. In a case series of aggressive pituitary adenomas, initiation of pasireotide in combination with continued temozolomide after transformation from an ACTH-silent to ACTH-secreting adenoma during temozolomide therapy led to biochemical control and tumor volume reduction in one case, while use of pasireotide monotherapy in another case of recurrent disease following temozolomide therapy led to biochemical control but not tumor volume reduction [107].

In summary, targeting SSTR5 and D2R with pasireotide and cabergoline, respectively, either alone or in combination, is a rational therapy directed to the disease etiology but not effective in all patients, in particular those with more severe hypercortisolism. Therefore, there is an unmet need for new, innovative pituitary-targeting drugs. Potential targets and compounds are discussed in the section New Targets, New Drugs.

3.2 Cushing's Syndrome Based on Adrenal Neoplasias

3.2.1 Benign Tumors and Hyperplasia

In patients with unilateral adrenal adenoma and CS in whom unilateral adrenalectomy is delayed by an underlying condition, adrenal steroidogenesis inhibitors can be used to control cortisol excess until surgery is possible [108, 109]. In patients with ACTH suppression, AI is more likely to occur with steroidogenesis inhibitors than in patients with ACTH-dependent CS, where reduction of cortisol negative feedback increases ACTH, which might increase cortisol and steroid precursors. Close monitoring of morning serum and 24-h urinary cortisol levels is indicated to titrate the dose of steroidogenesis inhibitors [67]. Not all medications are universally available or have regulatory approval, so the choice of drugs between ketoconazole, metyrapone, or osilodrostat can vary between countries [67]. Therapy for severe hypercortisolism with two or more steroidogenesis inhibitors has

been used in a few case reports and limited series [67, 110]. Metyrapone and osilodrostat are 11β-hydroxylase inhibitors and lead to accumulation of precursors with risk for hirsutism in women, hypokalemia, and hypertension [67, 71, 111]. Osilodrostat can cause AI even after drug discontinuation [80, 81]. In preliminary, small case studies, osilodrostat doses required to control hypercortisolism in patients with cortisol-secreting adenomas may be higher than in patients with CD [111–113].

3.2.2 Control of Cortisol Excess in ACC

In a significant proportion of patients with initial ACC or recurrent advanced disease, important cortisol excess can occur and requires vigorous therapy to reduce potential life-threatening morbidities, such as severe infection, thromboembolic disease, hypokalemia, and cardiometabolic complications; in addition, deleterious effect of hypercortisolism on the tumor immune environment confers worst tumor prognosis and response to systemic therapies [114, 115]. In ACC, mitotane is indicated both for its steroidogenic enzyme inhibition (relatively slow onset of action) and its cytotoxic and antiproliferative properties [114–116]. Mitotane is administered orally at 500 mg twice daily and increased up to 6 g daily, with regular determinations of serum mitotane levels, to reach a therapeutic range of 14–20 µg/mL while minimizing toxicity [114–116]. When cortisol excess becomes controlled, replacement with hydrocortisone is necessary, as mitotane induces hepatic cytochrome P450 enzymes and cortisol metabolism [117], with maintenance doses of hydrocortisone two to three times higher than normally used [114–116, 118]. In addition, mitotane increases corticosteroid-binding globulin (CBG), resulting in artefactual elevation of serum cortisol values [119]; 24-h UFC excretion remains the best index of adequate control or substitution of cortisol for such patients [114–116].

In patients with extreme hypercortisolism, other adrenal enzyme inhibitors are required in addition to mitotane [114–116]. There are no published large studies to determine which steroidogenesis inhibitors result in better control, but metyrapone has been used successfully in ACC; it is initiated at a dose of 250 mg four times daily and can be increased up to 6 g/day [114–116]. Ketoconazole may be less able to control hypercortisolism as a single agent in ACC, starting with 200 mg administered orally three times daily up to 1200 mg daily, but can be combined with metyrapone [120]. A recent series of seven patients with ACC and cortisol excess reported rapid control of hypercortisolism using osilodrostat at doses varying from 4–40 mg daily [76]. Similar to metyrapone, specific determination of cortisol levels (liquid chromatography-tandem mass spectrometry in blood or urine) is important to avoid cross-reactivity in immunoassays with the accumulation of the 11-deoxycortisol precursor which results from 11β-hydroxylase inhibition [71]. In severe, uncontrolled cases, addition of GR antagonism with mifepristone can be beneficial [121]. Eventually, aldosterone deficiency is replaced with addition of fludrocortisone (0.1–0.3 mg daily) and adjusted to restore normal blood pressure and serum levels of potassium and renin. If metyrapone or osilodrostat causes salt retention and hypertension, spironolactone, eplerenone, or amiloride can be used with other antihypertensive drugs if necessary with frequent serum potassium monitoring [114–116].

3.2.3 Therapy of Primary Bilateral Pigmented Micronodular Adrenal Dysplasia (PPNAD) or Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) Patients with Excess Cortisol Secretion

Usually, in the young patients with PPNAD and CS with or without Carney complex, bilateral adrenalectomy has been the most frequently utilized therapy requiring lifelong steroid replacement; only rarely was unilateral adrenalectomy successful in very mild cases [122–124]. In rare instances, medical therapy with steroidogenesis inhibitors was utilized in the short term while awaiting surgery [125] or even as long-term therapy [126, 127].

In patients with PBMAH and overt CS with elevated UFC, therapy is needed and includes adrenal surgery as first-line in most patients [7, 108, 128, 129]. While this has traditionally involved bilateral adrenalectomy, unilateral adrenalectomy with resection of the larger gland may be used in select cases with remission reported in nearly three-quarters of patients and long-term surveillance for progression of residual adrenal function needed [129]. For patients with mild dysregulated cortisol excess and normal UFC, indications for therapy follow adrenal incidentaloma guidelines without specific validation for PBMAH patients [130, 131]. In the presence of normal UFC, normal ACTH, cortisol less than 138 nmol/L (5 mcg/dL) following 1 mg dexamethasone test, and no hypercortisolism-induced comorbidities, monitoring without adrenal surgery is recommended [129–136]. Patients with bilateral adrenal lesions (probably PBMAH) presented with double the relative risk of deleterious cortisol excess and associated comorbidities [135].

3.2.4 Medical Therapy for PBMAH

Adrenal enzyme inhibitors such as ketoconazole and metyrapone can be efficient before adrenalectomy when severe hypercortisolism results in life-threatening morbidities, or when there is recurrence of hypercortisolism following unilateral adrenalectomy and completion adrenalectomy is not pursued [10, 131]. Ketoconazole was used in some PBMAH cases while awaiting further therapy [137, 138] or during long-term, low-dose therapy [139]. Metyrapone

was effective in two PBMAH patients in a large retrospective UK study [64] as well as in two Japanese patients with PBMAH including one woman treated for seven years without development of hirsutism [140, 141]. In a PBMAH patient, synergetic combination of ketoconazole and osilodrostat achieved good control of hypercortisolism [142]. In a limited, proof-of-concept study, therapy was adjusted with higher doses in the evening than during daytime to reset the cortisol nycthemeral rhythm and reduce the cardiovascular risk marker interleukin-6 [143]. Trilostane, a 3β-hydroxysteroid dehydrogenase inhibitor, partially suppressed cortisol production with clinical improvement but did not prevent PBMAH growth during a four-year treatment period [144]. Rare PBMAH patients were treated with mitotane [145]. In patients presenting with excess cortisol production in a cyclic manner, steroidogenesis inhibitors should be administered in a block and replace strategy with hydrocortisone in two to three split doses.

In a small series of four PBMAH patients with CS, the competitive GR and PR antagonist mifepristone induced clinical remission and reduced excess cortisol comorbidities in a median time of 5 months with fatigue as the most common side effect [146]; however, it is difficult to adjust therapy only on the basis of glucose and blood pressure improvement and clinical symptoms, while cortisol levels are not reliable markers of control.

3.2.5 Specific Pharmacological Therapies Targeting Aberrant Hormone Receptors

As cortisol secretion is regulated by aberrantly expressed G protein-coupled receptors (GPCRs) in 77–87% of PBMAH patients with modest or overt CS [129, 147], some specific pharmacological therapies to block the activation of the aberrant GPCRs were attempted (Fig. 2). In a few patients with glucose-dependent insulinotropic peptide (GIP)-dependent PBMAH, pharmacological blockade of postprandial release of GIP using the somatostatin receptor analogs octreotide or pasireotide was only transiently effective with escape within 1–3 months requiring an eventual adrenalectomy [148–152]. In the future, novel GIP receptor antagonists, such as GIP(3-30)NH2, could be an interesting therapeutic option for patients with GIP-dependent CS [129, 153–155]. In some patients with PBMAH and CS regulated by aberrant β-adrenergic receptors, β-blockers, such as propranolol or nadolol, can provide long-term control of hypercortisolism [129, 156–159]. However, only biochemical improvement is achieved in other patients without clinical benefit [160]. If β-adrenergic receptor antagonists are unable to completely normalize UFC, or if their use is limited by side effects such as bradycardia, unilateral adrenalectomy is suggested with maintenance of β-blockers to control production from the contralateral gland [129, 159, 161, 162]. This was also successful in one PBMAH case with combined CS and primary aldosteronism regulated by β-adrenergic and V1-vasopressin agonists in whom atenolol was efficient over 10 years until escape required adrenalectomy [163]. In PBMAH patients with luteinizing hormone (LH)/human chorionic gonadotropin (hCG)-dependent CS, administration of long-acting leuprolide acetate – a GnRH agonist – can suppress endogenous LH and allowed control of hypercortisolism for more than 10 years without CS progression [129, 160, 164–168] or of estrogen excess in another PBMAH case [169]; it may be necessary to replace lack of gonadal steroids and monitor bone density at regular intervals, especially in female patients before the age of menopause.

The arginine-vasopressin (AVP) receptor type I (AVPR1) and serotonin type 4 receptor (HTR4) are the two most prevalent aberrant GPCR regulating cortisol secretion in patients with PBMAH, but unfortunately, there are currently no available antagonists for these receptors [129, 147, 162]. Similarly, there are no available antagonists for the aberrant ligands in PBMAH tissues such as ACTH, but some novel antagonists are under clinical investigation for other indications and may become quite useful therapies in this setting in the future. Since in most PBMAH tissues excessive steroid production is regulated by several aberrant receptors together with locally produced ACTH, targeting may require combined therapies [129].

3.3 Cushing's Syndrome Based on Ectopic ACTH Syndrome

Cushing's syndrome due to ectopic ACTH secretion (EAS) is a severe condition associated with intense hypercortisolism in most cases [170, 171]. The overall prognosis for EAS is correlated with the type of underlying neoplasm and the mortality rate is far better in patients with resectable or occult, well-differentiated neuroendocrine tumors compared to patients with metastatic disease and/or poorly differentiated neuroendocrine carcinomas [172]. However, intense hypercortisolism associated with EAS is responsible for numerous life-threatening comorbidities in the short/mid-term (including major hyperglycemia, hypokalemia, prolonged QT, severe hypertension, cardiac insufficiency, pulmonary thromboembolism, opportunistic infections, psychosis, and gut perforation) and contributes to mortality [172, 173]. Ectopic ACTH secretion should be considered an endocrine emergency requiring rapid intervention combining symptomatic treatments of comorbidities (antibiotics, anticoagulation, potassium-sparing diuretics and potassium supplementation, antihypertensive therapy, insulin infusion, etc.), cortisol-lowering procedures, and treatment of the underlying neoplasm [170]. Depending on the patient's condition, treatment may be carried out in the ICU but in close collaboration with endocrinologists.

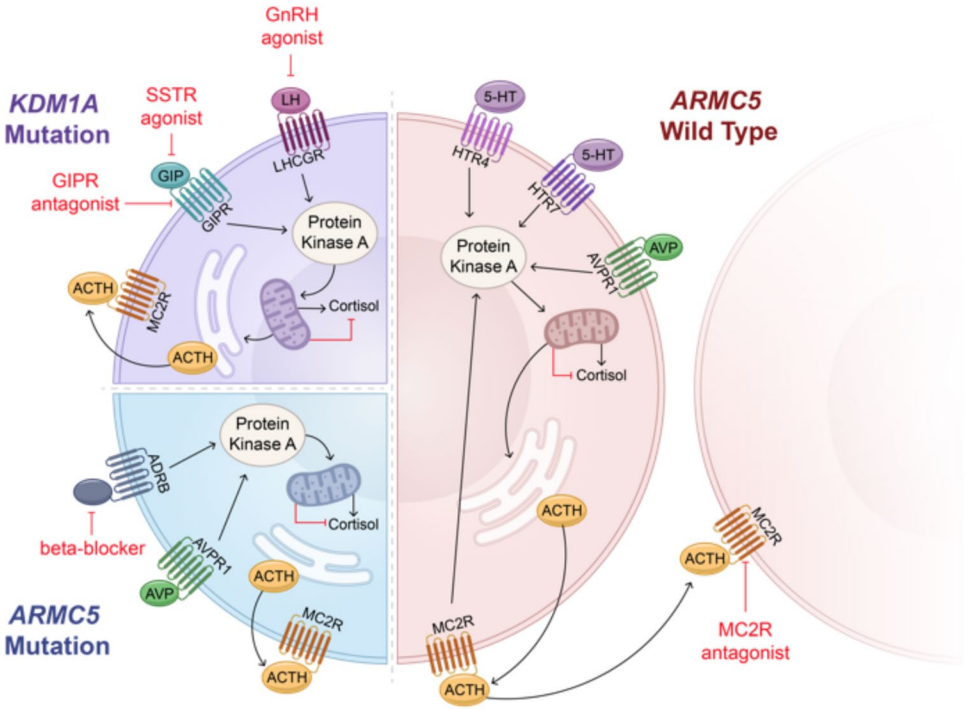

Fig. 2 Eutopic and ectopic hormone receptor expression in primary bilateral macronodular adrenal hyperplasia (PBMAH). While independent of pituitary adrenocorticotropic hormone (ACTH), cortisol secretion in PBMAH is governed by autocrine and paracrine signaling with the effect of activating the adenyl cyclase pathway via aberrantly expressed eutopic and ectopic G protein-coupled receptors (GPCRs). Ectopic ACTH production by the PBMAH cell activates its own or adjacent cell's melanocortin type 2 receptor (MC2R). Increased mast cells produce serotonin (5-HT) which activates the serotonin type 4 receptor (HTR4) and type 7 receptor (HTR7). Arginine-vasopressin (AVP) stimulates the arginine-vasopressin (AVP) receptor type I (AVPR1). In some *ARMC5* pathogenic variants, there may be overexpression of AVPR1 and β-adrenergic receptors (ADRB). In *KDM1A* pathogenic variants, glucose-dependent insulinotropic peptide receptor (GIPR) and more rarely luteinizing-chorionic gonadotropin hormone receptor (LHCGR) are over-expressed. Targeting these signaling pathways via GPCR antagonism or inhibition of ligand production can decrease cortisol secretion

Several therapeutic options can be used to control or reduce hypercortisolism, including surgical excision of non-metastatic tumors, antineoplastic chemotherapy for metastatic tumors, pharmacotherapy, and bilateral adrenalectomy. These options should be discussed within an experienced multidisciplinary team according to the patient's condition. However, and as recommended by the Endocrine Society, thanks to their effectiveness and rapidity of action, steroidogenesis inhibitors should be used as primary treatment [7], including in preparation for surgery of an ectopic tumor or in patients for whom bilateral adrenalectomy has been programmed. Steroidogenesis inhibitors can be used with two main strategies: rapid titration with increasing drug dosage according to the cortisol level, or with a "block and replace" strategy using an immediate high drug dosage to lower cortisol production to the range seen in AI followed by hydrocortisone (or other exogenous glucocorticoid) replacement [54]. This last strategy has the advantage of speed in controlling hypercortisolism, reduction in the number of cortisol measurements to monitor drug dosage, and prevention of AI in patients concomitantly receiving an effective antineoplastic therapy that may induce a rapid decrease in cortisol production [54]. Finally, cortisol-lowering medical therapy in EAS has the potential to reverse SSTR downregulation associated with cortisol excess and facilitate identification of occult tumors via somatostatin receptor scintigraphy or PET/CT with ^{68}Ga-DOTA derivatives once eucortisolism is achieved [174–176].

The steroidogenesis inhibitor etomidate has been successfully used in the short term and commonly produces a dramatic decrease in cortisol levels within 24–48 h. Given its intravenous administration, it may be useful when the oral route is not possible, such as in patients with vomiting, unmanageable symptoms (such as respiratory failure), or in patients with steroid psychosis [82–84, 170]. Due to its sedative/sub-hypnotic effect when given at relatively high dosage, etomidate should be used preferentially in the ICU.

Ketoconazole monotherapy has been used successfully in patients with EAS, although high doses (1000–1600 mg) are usually required and the rate of control of hypercortisolism is lower than in CD [170, 177, 178]. Liver enzymes are

frequently increased during severe hypercortisolism due to steroid hepatitis. This should not necessarily contraindicate the use of ketoconazole, and a decrease in liver enzymes, in parallel to the decrease in cortisol levels induced by ketoconazole, has been described [179].

In EAS, monotherapy with metyrapone has been more frequently reported than with ketoconazole and appears to be successful in the majority of cases [7, 64, 66, 180]. The dosage depends on the degree of hypercortisolism but usually ranges from 1500–6000 mg daily. At this dosage, metyrapone can induce a dramatic fall in cortisol levels within 72 h [66].

Since metyrapone and ketoconazole inhibit distinct steroidogenic enzymes, their synergistic action can be used to effectively treat intense hypercortisolism. In a published series of 14 cases of intense EAS, administration of high doses of these drugs (median starting doses of 2500 mg daily of metyrapone and of 1000 mg daily of ketoconazole), induced a decrease in median UFC, from 40 times to 3 times the upper limit of normal, after 1 week of treatment with 50% of patients showing normalized UFC [120]. The triple combination of mitotane (3.0–5.0 g daily) with high-doses of metyrapone and ketoconazole at the start has been reported in a small series [110]. The two latter fast-acting agents induced a dramatic decrease in UFC within 48 h with an improvement in clinical condition. The UFC remained controlled on this combination therapy. In some patients, metyrapone and ketoconazole could be discontinued after several months, as UFC excretion remained controlled owing to the delayed action of mitotane. This strategy may be useful specifically to avoid bilateral adrenalectomy in patients with occult ectopic ACTH-secreting tumors at presentation, while waiting for the tumor to be radiologically localized and removed. Thanks to its adrenolytic action, mitotane has been used by other groups while waiting for the characterization of initially occult tumors [86]. However, in almost all cases, mitotane induced AI (and thus was used in a block and replace strategy), and due to its delayed action, patients first required treatment for weeks to months with steroidogenesis inhibitors [86].

The recently introduced steroidogenesis inhibitor osilodrostat demonstrated efficacy in a retrospective French series of 33 patients with EAS and intense hypercortisolism [75]. Used initially as first-line monotherapy or following previous treatment with cortisol-lowering drugs, osilodrostat was able to normalize cortisol levels in 82% of cases and dramatically improved comorbidities. A high starting dosage (20–60 mg daily) was used in the most severe cases and was able to normalize or near-normalize UFC within 1–2 weeks. Treatment was well tolerated overall, but AI was the most frequent adverse event occurring in 24% of cases.

Tyrosine kinase inhibitors (TKIs) are an alternative to steroidogenesis inhibitors in the specific situation where a metastatic medullary thyroid carcinoma is responsible for EAS, since they may rapidly and fully control ACTH secretion (and consequently cortisol production) independent of a reduction in tumor size [170, 181]. Successful treatment of EAS in metastatic medullary thyroid carcinoma has been demonstrated with both multitargeted TKIs, such as vandetanib and sunitinib [181, 182], as well as selective *RET* inhibitors, such as selpercatinib [183, 184]. The ACTH-secreting neuroendocrine tumors may express functional SSTR2 and D2R. A few case reports have shown that octreotide and cabergoline, which target these receptors, may reduce ACTH secretion and hypercortisolism at least in the short term, but these drugs were unable to fully control hypercortisolism in most treated patients [7, 170]. Depending on the specific type and features of ACTH-secreting neuroendocrine tumor, other possible treatment options include peptide receptor radionuclide therapy, external radiotherapy, cytotoxic chemotherapy, radiofrequency ablation, and chemoembolization [170, 173]. The paucity of reports means it is difficult to accurately evaluate the effectiveness of the glucocorticoid antagonist mifepristone in this situation [121]. Limitations of mifepristone include overstimulation of mineralocorticoid receptors secondary to the blockade of the GR, which may worsen hypokalemia and hypertension, and the impossibility of monitoring drug efficacy using cortisol measurements [121].

4 New Targets, New Drugs

Increased understanding of the pathophysiology of pituitary adenomas has identified potential novel pituitary-directed targets for the treatment of corticotroph adenomas.

4.1 ACTH Receptor-Blocking Drugs

Blockade of the effect of excessive ACTH secretion in ACTH-dependent CS is an attractive option for the treatment of CD. Recently, several novel ACTH receptor, also known as melanocortin-2 receptor (MC2R), antagonists have been developed and tested in vitro and in vivo.

In an experimental AtT20 rat xenograft model of CD, as well as in a model with continuous ACTH administration, the nonpeptide selective ACTH antagonist CRN04894 induced a strong suppression of corticosterone levels [185, 186]. CRN04894 (Atumelnant) is currently being tested in a phase 1b/2a single-center study (NCT05804669), and preliminary promising results showed that this oral ACTH antagonist, administered once daily at a dose of 80 mg, induced a sustained suppression of serum cortisol and UFC in five patients with ACTH-dependent CS. An expected compensatory increase in ACTH was observed;

however, it did not result in loss of efficacy [187]. Moreover, preliminary data from a phase 2, open-label study in participants with classical congenital adrenal hyperplasia (NCT05907291) showed a profound, rapid, and sustained suppression of androstenedione and 17-hydroxyprogesterone in 100% of participants evaluated to date. There were no meaningful changes in ACTH, and serious AEs were not reported [188].

Another ACTH-blocking drug, a monoclonal antibody preventing the binding of ACTH to MC2R (ALD1613), has potent and sustained ACTH-blocking effects in vitro and in vivo in rats (mice) and monkeys [189, 190]. To the best of our knowledge, no clinical trials with this monoclonal ACTH antibody have been reported.

4.2 Ubiquitin-Specific Protease 8 (USP8) and Epidermal Growth Factor Receptor (EGFR) Inhibition

Gain-of-function mutations in *USP8* have been found in about 50% of corticotroph tumors, suggesting an important role in their pathophysiology [191, 192]. The *USP8* mutations result in increased deubiquitinase activity, reduced EGFR degradation, and increased EGFR signaling [193]. In corticotroph adenoma cells, this results in stimulation of POMC expression and tumor cell growth. Since approximately 50% of corticotroph adenomas express EGFRs, which stimulate POMC expression [194], it has been suggested that EGFR and USP8 inhibition may be a treatment target. Two USP8 inhibitors (RA-9 ((3E,5E)-3,5-bis[(4-nitrophenyl)methylene]-4-piperidinone) [195] and DUBs-IN-2 (9-oxo-9H-indeno[1,2-b]pyrazine-2,3-dicarbonitrile) [196]) induce apoptosis while inhibiting ACTH secretion and cell proliferation in cultured AtT20 pituitary tumor cells.

Two EGFR TKIs (gefitinib and lapatinib) were shown to inhibit corticotroph tumor size and proliferation, as well as POMC expression and ACTH secretion in vitro and in vivo [194, 197]. The efficacy of gefinitib is currently being tested in an ongoing clinical trial in patients with *USP8* mutated tumors (NCT02484755). Interestingly, corticotroph adenomas with mutated *USP8* tend to have a higher expression of SSTR5 and show a higher inhibition of ACTH secretion with pasireotide treatment in vitro [198, 199]. It remains to be confirmed whether patients with corticotroph adenomas harboring *USP8* mutations also respond better to pasireotide compared to patients with adenomas harboring wild-type *USP8* [200].

4.3 Cyclin E Inhibition

Selective increased expression of cyclin E has been found in corticotroph adenomas [201]. Moreover, activation of cyclin E stimulates cell proliferation and ACTH production in primary corticotroph pituitary adenoma cells [202]. The cyclin E inhibitor roscovitine was shown to induce cell cycle arrest and suppression of POMC expression in mouse corticotroph AtT20 tumor cells [203]. Based on these observations, the effect of R-roscovitine (seliciclib) was tested for the treatment of CD [204]. Participants with CD were treated with oral seliciclib 400 mg twice daily for 4 consecutive days per week for 4 weeks. Seliciclib decreased UFC by 42%, although none achieved normalization. Plasma ACTH decreased by 19% in participants who achieved 48% or greater UFC reduction, suggesting that seliciclib has pituitary-directed action. Adverse events were elevated creatinine, transiently elevated liver enzymes, and anemia. No follow-up clinical trials have been reported.

4.4 Heat Shock Protein 90 (HSP90) Inhibition

It is well documented that the chaperone HSP90 induces conformational changes of the GR resulting in altered transcriptional activity of the receptor. Moreover, increased expression of HSP90 is found in corticotroph adenomas, which may prevent functional activation of the GR [205]. Therefore, overexpression of HSP90 has been suggested to be involved in resistance to the suppressive effect of cortisol. HSP inhibition may restore negative feedback to cortisol [205]. The HSP90 inhibitor silibinin inhibits POMC expression and ACTH production in vitro and in vivo in a xenograft model of AtT20 corticotroph tumor cells as well as in primary cultures of human corticotroph adenomas [206–208]. Silibinin, alone or in combination with other drugs, has previously demonstrated anti-tumor action in many cancers, including prostate cancer, and appears to have a favorable safety profile [209]. To the best of our knowledge, no clinical trials in CD have been reported.

4.5 Histone Deacetylase (HDAC) Inhibitors

Many tumor types have aberrant histone modifications which can be involved in tumor initiation, tumor progression, metastasis, and sensitivity to drug treatment [210]. HDAC inhibitors increase histone acetylation, which can result in re-expression of silenced tumor suppressor genes or reduction in expression of oncogenes. Several HDAC inhibitors have been tested in experimental models of corticotroph tumors. HDAC inhibitors such as vorinostat, amongst others, as well as a dual phosphatidylinositol-3-kinase (PI3K)/HDAC inhibitor CUDC-907 inhibit cell proliferation and ACTH production in experimental models of corticotroph tumors [211]. However, despite their potential, this generation of epigenetic drugs has not yet been tested clinically in CD.

4.6 Targeting Retinoic Acid Receptor (RAR)

Retinoic acid (RA) binds with high affinity to the RAR and retinoid X receptor (RXR). RA inhibits POMC expression as well as ACTH and cortisol secretion and induces an upregulation of D2R expression in several experimental models of CD in vitro and in vivo [212–214]. In two clinical trials with a limited number of participants with CD, the effects of treatment with RA for 6–12 months were evaluated. Treatment with RA resulted in normalization of UFC in 43% and 37.5% of participants, respectively [215, 216]. The treatment was generally well tolerated. No subsequent clinical studies have been reported.

To summarize, in the development and testing of novel drugs and drug targets in CD, promising data from experimental models of CD exist. However, most of the novel drugs have not yet reached clinical testing of their effectiveness. While promising effects of RA have been demonstrated in experimental models of CD, RA does not appear that effective in patients with CD. On the other hand, the effects of MC2R antagonists in CD seem promising.

5 Conclusion

Medical therapy in CS is needed when patients are not candidates for or decline surgical intervention, there is residual or recurrent disease following surgery especially when repeat intervention is not possible or pursued, and finally, when used as bridge therapy preoperatively or while awaiting the effects of radiotherapy. Currently available medical therapy targets the corticotroph adenoma in cases of CD, acts to inhibit steroidogenesis at the level of the adrenal glands, or blocks cortisol's effects via GR antagonism. Medical therapy is tailored based on the source and degree of hypercortisolism as well as patient characteristics.

Declarations

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Conflicts of Interest Nidhi Agrawal is on the advisory board for Xeris, Amryt, Camurus, Crinetics, and Novo Nordisk and serves as a principal investigator on research trials for Amryt, Recordati, Ascendis, and Novo Nordisk. Antoine Tabarin has received speaker and board honoraria from Recordati and HRA Pharma. André Lacroix has received research grants and speaker fees from Pfizer Canada and Recordati Canada Rare Diseases, speaker fees from Medunik Canada, and royalties as an editor of the adrenal section of UpToDate and Encyclopedia of Endocrine Diseases and is a co-inventor on a patent for endocrine diseases related to *KDM1A* for work registered at the Universite Paris–Saclay. Richard A. Feelders has received speaker fees and research grants from Recordati and Corcept. Brendan R. Dillon, Yair Schwarz, Kristen Dancel-Manning, and Leo J. Hofland have no interests to disclose.

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